Author’s response to reviews

Title: Prevalance of BRCA1 and BRCA2 mutations in familial breast cancer patients in Lebanon.

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Author’s response to reviews:

Reviewer: 1

Q1: Perhaps the sequences of the primers and annealing temperature should be included in the manuscript (Discretionary Revisions).

R1: We mentioned in paragraph “BRCA1 and BRCA2 analysis’ that primers sequences are available on request as well as annealing temperature of each exons.

Q2: May arouse interest in drawing attention to the desirability of testing for differences in the prevalence of BRCA1/2 depending on the ethnic differences (Muslims, Christians). Hence, the authors question whether such tests have already been taken earlier? Such information could be included in the discussion (Discretionary Revisions).

R2: Testing a larger cohort will provide us with more information in order to distinguish between the prevalence of BRCA1/2 depending on the ethnic differences (Muslims/Christians) in the Lebanese population.

Reviewer: 2

Major compulsory revisions:

Q1: In Results, throughout the whole section and including Tables, there is confusion about the clearly deleterious mutations reported and the suspected deleterious variants. In detail, it is stated in paragraph 2 that “Five confirmed disease-associated BRCA1 mutations and two confirmed disease-associated
BRCA2 mutations were found in this cohort, however in Table 1 only the nonsense mutation W1815X (found x2) is reported as clearly deleterious, and the two missense mutations C44F (found x2) & P142A (found x1) are designated by asterisks as “considered deleterious”, which in my mind is not the same as “confirmed deleterious”. Moreover, there is no justification in the following paragraph (Results, paragraph 3) for this classification (references proving pathogenicity) other than the vague family information. In fact, there is an abundance of evidence in the bibliography towards the pathogenicity of the first mutation (p.C44F, a RING-finger domain mutation), both functional and in silico, but very little evidence exists for p.P142A. These references should be retrieved and mentioned. Also, it is advised that pedigrees should be included for these 3 families and, if possible, segregation analysis of the variants should be performed to show co-occurrence with the disease.

R1:
A- As suggested by the reviewer, the expression “confirmed deleterious” was corrected in paragraph 2.
B- As for the p.C44F and p.P142A mutations references and the pedigrees, these were added as suggested by the reviewer.
C- Co-segregation analysis of the variants within the families was not performed because of the reluctance of the families or the non accessibility of other family members.

Q2. In concordance to the above, it should be clear in Tables 1 and 2 which are the definitely deleterious and which are the suspected deleterious mutations. Maybe a separation of all genetic variation found in three categories (deleterious, unclassified variants, known polymorphisms) should help make the Table data more clear.

R2: This point was clarified in the table 1 legend.

Q3: Reference also needed for BRCA2 mutation causing exon skipping (Results paragraphs 4 and 5).

R3: The references were added as suggested by the reviewer.

Minor essential revisions:
Q1: In Introduction, end of paragraph 3, there is a much more recent reference that I believe should be used instead (or together with) ref. 8: Lakkis NA, Adib SM, Osman MH, Musharafieh UM, Hamadeh GN, ‘Breast cancer in Lebanon: incidence and comparison to regional and Western countries’, Cancer Epidemiol 2010, 34(3):221-5. According to this, median age for breast cancer onset in Lebanon is 52.5 years.

R1: The reviewer was right concerning the use of a more recent reference in this paragraph. Thus, we have replaced it by the suggested reference.
Q2: In Discussion paragraph 1 ‘deleterious or pathogenic’ should be either ‘deleterious’ or ‘pathogenic’.

R2: Replaced by “deleterious” in paragraph 1.

Discretionary revisions:

Q1: Discussion is in general well justified. One additional comment may be on the possible existence of founder mutations in the Lebanese population. Testing a larger cohort for the two mutations found to recur in your population (BRCA1 p.C44F & p.W1815X) could be a good start.

R1: Added in the last paragraph in the discussion.